PHARMACEUTICAL TARGETS IN GER ANY

COMBINED INTELLIGENCE OBJECTIVES
SUB-COMMITTEE

LONDON—H.M. STATIONERY OFFICE

PHARMACEUTICAL TARGETS

Nordmark Werke - Utersen, Germany
I.G. Farben - Leverkusen, Germany
I.G. Farben - Hochst, Germany
Behringwerke - Marburg, Germany
E. Merck - Darmstadt, Germany

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Medical

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Introduction

The plants visited, namely, Nordwark Werke, Utersen, I.G.Farben Pharmaceutical, Leverkusen, I.G. Farben Pharmaceutical, Höchst, Behringwerke Biological, Marburg and the E. Merck Pharmaceutical, Darmstadt, are all operating in a limited way under military control.

The equipment in all of them does not very in many respects but some firms use better manufacturing technique than others, and these are described in the reports.

A great amount of manual labor is utilized, mainly due to the low wage rates. As an example, girls in finishing and in other departments in the plants are paid 20/30 reichmarks per week.

In the plants visited, men having more than one department under their direction hold a degree of Ph.D. in chemistry and pharmacy. Department heads, that is men in charge of a single department, have a degree Ph.D. in pharmacy.

The larger German pharmaceutical manufacturers do not make or sell pharmacopical products, but confine their efforts only to specialty or trade marked items. They, therefore, do not have the extensive amount of equipment necessary to manufacture fluid extracts, elixers and other products of like nature. The products are mainly the results of research in the fields of synthetic and biological chemistry.

All the plants visited, allot a large amount of floor space to all operations in the pharmaceutical departments. Control methods in most instances do not compare with those in general practices in other countries. They do, however, attempt a type of analytical control over all of their products.

Nordmark Werke - Utersen, Germany

This plant was formerly located in Hamburg, but after being completely bombed out was moved to the town of Utersen about 25 K northwest of Hamburg, and at the time of our inspection was again just getting certain departments started into operation.

We interviewed Dr. Julius Wolfe, the manager, who showed us the plant. As we arrived rather late on Saturday, the plant was not in operation. It can only operate part time since coal and gas are not available in sufficient quantity to permit full scale production.

We were particularly interested in equipment and machinery for manufacturing pharmaceutical production of which this firm had only

a limited quantity. The report will deal with our observations by departments.

Ampoules

Preparation of solutions for ampoule filling is carried out in the conventional way, using sterile containers and several filtrations to insure clear solutions. Double distilled water, freshly prepared daily in glass stills, is used for the purpose.

Empty sealed ampoules are delivered by the glass manufacturers to the plant and it is assumed by this manufacturer that they are sterile, therefore no pre-cleaning operation is carried out before filling. Practically all ampoule filling was being done on four automatic machines which cut the empty ampoules to the desired length, fill a predetermined amount of solution by means of syringes to which are attached needles, and seal the ampoules by means of four gas jets.

The sealed empty ampoules are placed in individual cups by an operator, which clamp the ampoule into place, holding them rigid in a center position while all of the operations are performed. The cups are arranged in a circle and at a given point discharge the completed ampoule into a container on the side of the machine.

The filled ampoules are then labeled in a separate operation by means of semi-automatic printing and baking machines, then sterilized by autoclaving.

Both the ampoule and labeling machines are manufactured by:

Luigi Marzocchi
Via Natale Battaglia
Milan, Italy

No blueprints of the machines were available, but photographs will be taken and submitted to G (T) and 6W Branch, 21st Army Group Headquarters.

Ampoules are sorted by examination over diffused light for foreign material and packaged by hand operations.

Tablets (Compressed)

This firm being a small one in this respect were just installing three machines for the manufacture of tablets, since it was necessary to vacate part of the property to house soldiers.

They did, however, have a machine for the packaging of tablets in paper board boxes. It was not in operation, so we had no opportunity to observe its mechanical ability. It would package one size and shape tablet and was not adjustable. The machine was manufactured by:

Berlin Karlsruher Industrie Werke
Karlsrhue, Baden

General Comment

This plant has continuous distilling equipment with a capacity of 700L per hour evaporation at 30°C, which is not new or outstanding in any respect. They were also using a John Uri Lloyd type of still, which evaporates liquids from the surface. Equipment of this type has been in use in the United States for a great many years.

The remainder of the plant equipment presented to us nothing new in any respect.

I. G. Farben Industrie Pharmaceutical Plant - Leverkusen

Men interviewed were: Dr. Wingler, Dr. Wolferts, Dr. Neubert, Mr. H. C. Schuh

Ampoule Manufacturing

Solution Preparation

Solutions of chemicals for ampoule manufacturing are prepared in sterile bottles, with freshly double distilled water, and filtered three times, twice through paper and once through glass, to insure clarity and freedom from foreign particles before filling.

The distilled water used was made in conventional type stills, except that the lining of the still, the condensor tubes and all pipe lines carrying this type water are silver lined. The Germans claimed that silver was used because of its bacteriostic properties and that ph 6 to 6.2 could be better maintained. No test for pyrogenic substances is carried out by this laboratory.

Empty Ampoule Preparation

Empty sealed ampoules are delivered to the manufacturer who cuts the stem of the ampoule to the correct length on a hand machine, using a carborundum stone for the purpose. The ampoules are placed in rectangular racks, holding about 200, with the necks down. They are washed once only by placing the entire rack under a

vacuum bell containing distilled water. The vacuum is turned on the ampoules filled with water, then they are moved to another vacuum bell for withdrawal of the water. The ampoules are then placed in metal containers for hot air drying and sterilizing in an oven electrically heated and are stored in these containers until ready for use on the filling machines.

Ampoule Filling

This operation is of four types; (a) filling solutions by automatic machinery, (b) vacuum filling to a certain height, (c) filling solutions aseptically, (d) filling of dry powders.

(a) Filling Solutions is carried out on nine automatic and semi-automatic machines known as Makro-Roto, used for 1-2 c.c. sizes, and Auto-Roto for 5 cc and larger sizes. The machines were manufactured by Mayer of Aachen. The empty ampoules are placed on a rotary conveyer by the operator and fed into a ring which carries them to an individual label-printing machine, and back into the cycle of operation for baking the ink on the ampoule by means of electrical heat. It is then carried to the centering and filling station where a measured amount of solution is injected automatically through syringes, then sealed by four gas jets. Output of the machines is 18-20 per minute.

(b) Vacuum Filling. This operation consists of placing a quantity of ampoules in frames under a vacuum bell and filling to a given height. It was claimed that the glass ampoules were of sufficient accuracy in diameter that very little variation existed between individual filled ampoules. Ten percent excess solution was used to insure the proper amount in each container.

(c) Aseptic Filling. This type of work was carried out by a hand operation on glass hooded tables, the usual precautions being taken to insure sterility. Biological tests were applied to the filled ampoules.

(d) Filling Dry Powder. Evipan was being filled by hand methods. The dry substance was weighed in proper amounts on a special balance and filled into a widemouthed ampoule. This was partially sealed by hand, the ampoule evacuated 20 to 30 m.m. mercury and sealed by hand.

Tablet Manufacturing

This plant has quite an extensive department for this purpose, having a total of fifty machines of both single punch and rotary punch variety in operation. The rotary punch machines range in size

from 39 to 45 punches. The single punch from one to four punches per die.

Granulation of Material

This operation consists of two types; (a) with water or other liquid materials, (b) dry preparation.

(a) This operation is of the same type as used in the United States. Material is united with water or starch paste, forced through a screen on to trays and dried in hot air drying cabinets, ground to proper size, mixed with excipient or disintegrating materials, and are then ready for compressing.

(b) This operation consists of first running the dry chemical through very close set steel rolls to condense it, then mixed with excipients in rotary drums, ground in communiting machines, and compressed on large machines into slugs. The slugs are again ground to proper size granules and the material is then ready for compressing into tablets.

All of the compression machines were manufactured by Horne of Wörms. They are quite heavy in construction and apparently have been in use in this plant for a considerable period of time. Machines are set aside for the manufacture of individual items and are rarely changed from item to item. The size and weight of tablets are controlled by checking at frequent intervals on a Torsion spring balance built for the purpose.

Pills

The machinery for this operation is old and antiquated, nothing of any importance, mostly hand operated.

Coating Equipment

The usual type of rotary drums are in use in this plant for sugar, gelatin, silver and graphite coating of pills and tablets. Nothing new.

Packaging of Pharmaceutical Products

All packaging in this plant is hand work.

Behringwerke-Biologicals - Marburg

This firm produces biological products from both horse and ox blood so that the procedures described below may apply to either animal.

The stables were small one-story buildings with cement floors, wooden construction, tile roofs and with their twenty stalls separated by suspended four-inch logs. The feed pans and hay container were iron and were filled by a groom who would enter from the rear of the animals.

The animals were in very good condition and weighed approximately 1000-2000 pounds. When they were to be bled or innoculated they were brought from the stables to an outside, sheltered hitching rack to wait their turn. All animals not in good condition had been eliminated.

The bleeding and innoculating room was unique in that the entrances to the six stalls were made by opening the doors in the side of the building and leading the animal into a stall just inside and then closing the door. This left the animal with its head facing the center of the room.

The injections were made by gravity flow of the antigen from a separatory funnel. The rate of flow was assisted by lightly tapping or massaging the area of injection. Sterile cotton pads were placed over the point of injection when the needle was withdrawn.

The general scheme of injection for a horse on bleeding for Diphtheria was an initial dose of 200 cc of toxoid the first day, rest the second day, 400 cc the third day, rest the fourth day, 800 cc the fifth day, and then seven straight days of rest.

The blood was drawn as serum into a series of 500 cc glass cylinders. The volume of the bleeding varied from three to 5000 cc according to the weight of the horse. After one day's rest the horse was bled again. This was done for a series of four or five bleedings. If the animal showed signs of collapse, 1000 cc of Peristone was given intravenously. The cycle was completed by giving the animal a rest of eight days. It was claimed that the horses and oxen lived for two years under treatment.

The treatment is essentially the same for all antitoxic sera. (See list of sera in a previous report). The average Diphtheria serum potency was 5-600 units. Tetanus serum was a little higher.

Diphtheria antitoxin from the oxen and sheep were concentrated by pooling the sera of similar bleedings, diluting with distilled water and precipitating at 50% $(NH_4)_2SO_4$ using the saturated solution. This precipitate is removed by filtering on hard paper either on Buchner funnels by a vacuum or by gravity on regular funnels. The discard filtrate containing the albumen is used

as a fertilizer.

The sulphate precipitate of antitoxin was dissolved in a minimum of distilled water and dialysed in cellophane tubes for 24 hours in running water. The major portion of the remaining sulphate along with the natural electrolytes are now removed by electrodialysis. The Ph is maintained at 5.9 to 6.0 during the six hour dialysis by using a sheet of parchment paper as one membrane and a square of heavy cloth treated with a paste of glycerine, potassium bichromate and gelatine as the other. This equalize the flow of cations and anions (Law of Hitlorf). The dialysate is now collected into ten liter bottles and allowed to stand overnight. The liquid is finally clarified by centrifugation in a large eight bucket centrifuge, each container holding 1000 cc. The clarified antitoxin is decanted off, made 0.85 Na CL and 0.05% Phenol. It is adjusted to 10-12% total solids or as indicated by potency requirement. 80% unit recovery is claimed. The final product is decidedly brown but is said to remain clear from precipitate "indefinitely." The Ph is adjusted to Ph 7.0 to 7.2. The sterility is established by filtration thru a Seitz filter.

Horse sera is purified by the pepsin digestion method. A solution of pepsin, sera and distilled water is titiated to Ph 4.2-4.3 using citric acid. This stands at 40-46°C for 24 hours. Then it is filtered on paper. The antitoxic filtrate is made 55% $(NH_4)_2SO_4$ and filtered. The precipitate is now dissolved in a minimum of distilled water and dialysed in cellophane tubes for 24 hours. The major portion of the remaining sulphate is removed by electrodialysis. The dialysate is made 1% charcoal and allowed to stand overnight. The charcoal is removed by a Sharples centrifuge. It is Seitz filtered, made 0.85% Na Cl, titiated to Ph 7.0 to 7.2 using sodium bi-carbonate and 0.05% phenol added as a preservative. The total solids cannot exceed 12%. Dilution is made according to solids and potency.

It was claimed that 70-80% total solids were eliminated during concentration with only a 20-30% unit loss. Anti-toxin carries a three year expiration dating period and 10% excess is added to maintain the required potency level.

Antiphneumoccus sera are concentrated by the Felton method.

Summary

1. Final products are inferior in many respects to those produced by several U. S. firms.

2. Their theory of electrodialysis is excellent.

3. Concentration by pepsin digestion offers several decided advantages.

4. Diphtheria potency is very low.

5. Arrangement of equipment could be greatly improved.

6. Those in charge were superior workers.

Filling and Finishing of Biologicals

Filling. So far as we were able to determine, the German biological manufacturers did not package their products in multiple dose packages but in single dose glass sealed ampoules. This procedure is carried out in a separate room, one for each product. These rooms, however, are not sterile nor is any attempt apparently made to use sterile air as the outside windows of the room were open. A sterile technique of a type is used in filling by the use of a glass bell covered needle which is flamed at frequent intervals. The necks of the empty ampoules, previously cleaned with distilled water and sterilized with dry heat, are also flamed. The ampoules are immediately sealed with a flame by an additional operator.

Germany apparently did not have any national regulatory bureaus such as the U.S. Food and Drug Administration and the Institute of Health to set up working procedures and processes or to set up standards of purity for the manufacturers finished products.

Finishing. All labeling and packaging of filled packages was being done by hand, mainly because of cheap labor.

Remarks

This plant is now being operated by the Germans under the competent direction of a team of U.S. Army bacteriologists and biochemists placed in the plant by the Production Control Agency.

I. G. Farben Industrie Pharmaceutical Plant - Höchst

This plant in addition to manufacturing a line of pharmaceutical specialties in the form of ampoules and tablets also manufacture and package insulin. The procedure and equipment will be briefly described in the following report.

Ampoule Manufacturing

Empty Ampoule Preparation

Several methods of washing, drying and sterilizing ampoules

were used:

(a) The method of washing small ampoules by means of the vacuum bells was being practiced. This is the same procedure as used in Leverkusen.

(b) A machine with projecting stems on a long cylinder is used for injecting filtered steam into the ampoule for cleaning and sterilizing. The ampoules were placed on the stems by hand cleaned, placed containers and dryed in hot air ovens.

(c) A machine in which the ampoules were placed in a receptacle having partitions for each container, the receptacle placed over stems which were injected into the ampoule by a foot lever. Live filtered steam and water was introduced for cleaning and sterilizing purposes, hot air drying.

Solution Preparation

Chemicals are dissolved in the appropriate vehicle in previously sterilized containers and filtered twice, once through paper and once through glass filtering material to insure clarity. Biological products were filtered through Seitz filters. The solutions remain in the containers ready for filling. Two enamel lined stills with ceramic pipe and valves were used for the preparation of larger quantities of solutions. Double distilled water freshly prepared is used for all solution preparation.

Filling Operation

Several types of filling equipment is used; (a) vacuum filling, (b) automatic and semi-automatic filling, (c) hand filling, (d) closed system vacuum filling.

(a) Vacuum filling in this plant consists of placing the solution in a bell vacuum container, a receptacle containing the previously prepared empty ampoules, filling to a given height, sealing by hand and sterilizing by autoclaving. Several machines were developed by the head of the Höchst plant for larger operations, but the principle of operation is the same.

(b) Automatic and semi-automatic filling was accomplished by the use of Makro-Roto and Auto-Roto machines, the operation of which is described in the report on Leverkusen.

(c) Hand filling consists of filling a measured amount of solution from the container through a syringe into the ampoule.

(d) The closed system vacuum filling apparatus is a complicated

patented process for handling materials that are readily oxidizable, such as adrenalin and novocaine. The apparatus consists of a salt solution preparation kettle, a salt solution storage kettle, an intermediate chamber for dissolving the active ingredient, and a vacuum filling chamber. This apparatus uses nitrogen or can be used with any inert gas that will prevent oxidation. A blue print and patent description was requested. These are at Heidelberg.

Insulin Filling

Insulin is filled in a special constructed air conditioned room, lined with light metal painted with a material to which the dust in the air adheres. The filling tables are of special construction, plate glass with stainless steel trim with no connection between the filling operator and sealing except a small cover stainless steel turn-table. The greatest degree of sterile conditions are maintained. Germany permits a five-year dating on Insulin. The several types and the processes of manufacture will be described in another report.

Salvarsan Filling

This plant fills salvarsan on a special machine developed and patented by the Höchst plant. Each morning, or when a new lot of material is to be filled, the density is determined and the machine adjusted to fill a certain volume equal to a given weight. Blue prints were requested. After filling, the ampoules are partially sealed by hand, the air exhausted by a vacuum apparatus and sealed by hand. The sealed ampoules are tested by running them through a dark room on a conveyor, a high frequency current passed through them to determine leakers. Leaking ampoules will show a faint blue or green spark, tightly sealed ampoules---no spark.

Tablet Manufacturing

No outstanding granulation procedures or equipment is used in this plant.

Compression machine numbering sixty are of the same design and type as those described under Leverkusen, the same procedures and practices are used in this plant.

Packaging. The packaging of ampoules, insulin vials and tablets is all hand work.

E. Merck & Co. - Darmstadt

This plant was very badly damaged by bombing. It has been estimated that about 70% of the plant is destroyed, however, the

pharmaceutical manufacturing section was very little damaged. The units consist of a series of six one-story brick buildings completed in 1939. Like all other German manufacturing plants visited, Merck has alloted a large amount of floor space to their operations. This firm, unlike the others visited, have divided the buildings into individual rooms in which is processed one item only to avoid accidental contamination of products.

Ampoule

Empty Ampoule Preparation

Ampoules are delivered to Merck sealed. These are cut on a machine to the proper length, using a carborundum stone for the purpose. They are dried in electric ovens at 300°C for ten minutes.

They are all cleaned with distilled water by the vacuum bell method, that is, placing ampoules into metal racks or boxes and forcing water into them by vacuum and exhausting it in the same manner.

Solution Preparation

Merck prepare their solutions in the same manner as other firms--in sterile containers, using double distilled water made in silver lined equipment, filtering through paper and glass.

Ampoule Filling

Two methods of filling are in use; (a) vacuum filling to a height, (b) automatic filling.

(a) The vacuum filling has been described in the report made under I. G. Farben, Leverkusen. The Merck output by this method is 2500 per hour exclusive of labeling. A 10% excess is placed in each ampoule and the variation on testing will run between 1.1 c.c. to 1.3 c.c.

(b) This firm uses the Makro-Roto machine manufactured by Meyer of AAchen, which produces 6000 to 8000 filled, sealed and labeled ampoules per eight-hour day.

All ampoules are sterilized after filling at 100°C at .2A pressure for 30 minutes and are considered sterile, no tests being made biologically to determine sterility.

Tablet Manufacture

Granulating

The mixing of the chemicals with water or other granulating

medium in most instances is done by hand in small lots in stainless steel pans. A few items in larger size lots are mixed in stainless steel dough mixers. The moist material is then forced through an upright mechanical sieve, collected on trays and dried in electric ovens. Granulation operations are carried out in individual rooms with the name of the substance placed on a large label attached to the outside of the room. Equipment, including stainless steel mixers, granulators, and electric ovens, is duplicated many times. The materials when dry are ground to proper size into closed containers and is ready for compressing.

Compressing

The compression room is broken up into individual rooms or alcoves, one machine per room or alcove with a label in a prominent place so no mistakes can be made by the men handling this operation. Some of the rooms are completely enclosed with opaque glass to cut off light for the manufacture of tablets of light sensitive material. 35 compression machines were in operation.

Liquid Preparations

This firm manufactures one galemical preparation, namely, optonicum ephedrine syrup. The percolators, manufacturing and blending tanks and equipment were all of stainless steel. Nothing special or outstanding about this equipment.

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